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WO 01/78740 A1

(54) Title: MEDICAL COMBINATIONS COMPRISING MOMETASONE AND SALMETEROL

(57) Abstract: The present invention is concerned with pharmaceutical formulations comprising a combination of salmeterol and mometasone and the use of such formulations in medicine, particularly in the prophylaxis and treatment of respiratory diseases.

MEDICAL COMBINATIONS COMPRISING MOMETASONE AND SALMETEROL

The present invention is concerned with combinations of salmeterol and mometasone, particularly compositions containing a combination of salmeterol and mometasone and the use of such compositions in medicine, particularly in the prophylaxis and treatment of respiratory diseases.

GB 2 140 800 describes phenethanolamine compounds which are β_2-adrenoreceptor agonists including 4-hydroxy-α^1-[[[6-(4-phenylbutoxy)hexyl]-amino]methyl]-1,3-benzenedimethanol 1-hydroxy-2-naphthalenecarboxylate (salmeterol xinafoate) which is now used clinically in the treatment of bronchial asthma and related disorders.

EP 57,401 and US 4,472,393 describe mometasone i.e. 9,21-dichloro-11β,17-dihydroxy-16α-methylpregna-1,4-diene-3,20-dione, esters thereof such as mometasone furoate i.e. (11β,16α)-9,21-dichloro-17-[(2-furanylcarbonyl)oxy]-11-hydroxy-16-methylpregna-1,4-diene-3,20-dione, and pharmaceutical formulations thereof. Mometasone is an antiinflammatory corticosteroid, which is now used clinically in the treatment of respiratory disorders.

Although salmeterol xinafoate and mometasone furoate are effective therapies, there exists a clinical need for asthma therapies having potent and selective action and having an advantageous profile of action.

Therefore, according to the present invention there is provided a combination of salmeterol or a pharmaceutically acceptable salt, solvate, or physiologically functional derivative thereof and mometasone or a pharmaceutically acceptable salt, solvate, or physiologically functional derivative thereof.

It will be appreciated that the compounds of the combination may be administered simultaneously, either in the same or different pharmaceutical formulations or sequentially. If there is sequential administration, the delay in administering the second compound should not be such as to lose the beneficial therapeutic effect of the combination.

According to a further aspect of the present invention, there is provided a pharmaceutical formulation comprising salmeterol or a pharmaceutically acceptable salt, solvate, or physiologically functional derivative thereof and mometasone or a pharmaceutically acceptable salt, solvate, or physiologically functional derivative thereof, and a pharmaceutically acceptable carrier or excipient, and optionally one or more other therapeutic ingredients. According to a preferred aspect of the present invention, there is provided a pharmaceutical formulation comprising salmeterol xinafoate and mometasone furoate (suitably as in the form of the monohydrate), and a pharmaceutically acceptable carrier or excipient, and optionally one or more other therapeutic ingredients. In the most preferred aspect, the above pharmaceutical formulations are suitable for administration by inhalation.

It is to be understood that the present invention covers all combinations of particular and preferred aspects of the invention described herein.

As would be appreciated by the skilled person, salmeterol includes an asymmetric centre, and mometasone contains several asymmetric centres. The present invention includes both (S) and (R) enantiomers of salmeterol either in substantially pure form or admixed in any proportions, as well as each isomer of mometasone either in substantially pure form or admixed in any proportions. The enantiomers of salmeterol have been described previously, for example, in EP0422889 and WO 99/13867.

By the term "physiologically functional derivative" is meant a chemical derivative of salmeterol or mometasone having the same physiological function as the free compound, for example, by being convertible in the body thereto. According to the present invention, examples of physiologically functional derivatives include esters.

Suitable salts according to the invention include those formed with both organic and inorganic acids. Pharmaceutically acceptable acid addition salts include but are not limited to those formed from hydrochloric, hydrobromic, sulphuric, citric, tartaric, phosphoric, lactic, pyruvic, acetic, trifluoroacetic, succinic, oxalic, fumaric, maleic, oxaloacetic, methanesulphonic, ethanesulphonic, p-

toluenesulphonic, benzenesulphonic, isethionic, and naphthalenecarboxylic, such as 1-hydroxy-2-naphthalenecarboxylic acids.

Pharmaceutically acceptable esters of salmeterol or mometasone may have a hydroxyl group converted to a C_{1-6}alkyl, aryl, aryl C_{1-6} alkyl, hetaryl (such as furanyl) or amino acid ester.

As mentioned above, both salmeterol and mometasone and their pharmaceutically acceptable salts, solvates, and physiologically functional derivatives have been described for use in the treatment of respiratory diseases. Therefore, formulations of salmeterol and mometasone and their pharmaceutically acceptable salts, solvates, and physiologically functional derivatives have use in the prophylaxis and treatment of clinical conditions for which a selective β_2-adrenoreceptor agonist and/or an antiinflammatory corticosteroid is indicated. Such conditions include diseases associated with reversible airways obstruction such as asthma, chronic obstructive pulmonary diseases (COPD) (e.g. chronic and wheezy bronchitis, emphysema), respiratory tract infection and upper respiratory tract disease.

Accordingly, the present invention provides a method for the prophylaxis or treatment of a clinical condition in a mammal, such as a human, for which a selective β_2-adrenoreceptor agonist and/or antiinflammatory corticosteroid is indicated, which comprises administration of a therapeutically effective amount of a combination of salmeterol or a pharmaceutically acceptable salt, solvate, or physiologically functional derivative thereof and mometasone or a pharmaceutically acceptable salt, solvate, or physiologically functional derivative thereof. The present invention further provides a method for the prophylaxis or treatment of a clinical condition in a mammal, such as a human, for which a selective β_2-adrenoreceptor agonist and/or antiinflammatory corticosteroid is indicated, which comprises administration of a therapeutically effective amount of a pharmaceutical formulation comprising salmeterol or a pharmaceutically acceptable salt, solvate, or physiologically functional derivative thereof and mometasone or a pharmaceutically acceptable salt, solvate, or physiologically functional derivative thereof, and a pharmaceutically acceptable carrier or excipient. In a preferred aspect, there is provided such a method which

comprises administration of a therapeutically effective amount of a pharmaceutical formulation comprising salmeterol xinafoate and mometasone furoate (suitably as the monohydrate), and a pharmaceutically acceptable carrier or excipient. In particular, the present invention provides such methods for the prophylaxis or treatment of a disease associated with reversible airways obstruction such as asthma, chronic obstructive pulmonary disease (COPD), respiratory tract infection or upper respiratory tract disease.

In the alternative, there is provided a combination of salmeterol or a pharmaceutically acceptable salt, solvate, or physiologically functional derivative thereof and mometasone or a pharmaceutically acceptable salt, solvate, or physiologically functional derivative thereof, for use in therapy, particularly for use in the prophylaxis or treatment of a clinical condition for which a selective β_2-adrenoreceptor agonist and/or antiinflammatory corticosteroid is indicated. In particular, there is provided a pharmaceutical formulation comprising salmeterol or a pharmaceutically acceptable salt, solvate, or physiologically functional derivative thereof (suitably, salmeterol xinafoate) and mometasone or a pharmaceutically acceptable salt, solvate, or physiologically functional derivative thereof (suitably, mometasone furoate optionally in the form of the monohydrate), and a pharmaceutically acceptable carrier or excipient for use in therapy, particularly for use in the prophylaxis or treatment of a clinical condition for which a selective β_2-adrenoreceptor agonist and/or antiinflammatory corticosteroid is indicated. In a preferred aspect, the invention is concerned with the prophylaxis or treatment of a disease associated with reversible airways obstruction such as asthma, chronic obstructive pulmonary disease (COPD), respiratory tract infection or upper respiratory tract disease.

The amount of salmeterol and mometasone, or a pharmaceutically acceptable salt, solvate or physiologically functional derivative thereof which is required to achieve a therapeutic effect will, of course, vary with the particular compound, the route of administration, the subject under treatment, and the particular disorder or disease being treated. As a monotherapy, salmeterol xinafoate is generally administered to adult humans by aerosol inhalation at a dose of 50mcg or 100mcg twice daily.

While it is possible for the active ingredients of the combination to be administered as the raw chemical, it is preferable to present them as a pharmaceutical formulation. When the individual compounds of the combination are administered separately, they are generally each presented as a pharmaceutical formulation as described previously in the art.

Pharmaceutical formulations are often prescribed to the patient in "patient packs" containing the whole course of treatment in a single package. Patient packs have an advantage over traditional prescriptions, where a pharmacist divides a patient's supply of a pharmaceutical from a bulk supply, in that the patient always has access to the package insert contained in the patient pack, normally missing in traditional prescriptions. The inclusion of a package insert has been shown to improve patient compliance with the physician's instructions and, therefore, lead generally to more successful treatment. It will be understood that the administration of the combination of the invention by means of a single patient pack, or patient packs of each component compound, and containing a package insert instructing the patient to the correct use of the invention is a desirable additional feature of the invention.

Hereinafter, the term "active ingredients" means salmeterol or a pharmaceutically acceptable salt, solvate, or physiologically functional derivative thereof, preferably salmeterol xinafoate, and mometasone, or a pharmaceutically acceptable salt, solvate, or physiologically functional derivative thereof, preferably mometasone furoate.

Suitably, the pharmaceutical formulations which are suitable for inhalation according to the invention comprise the active ingredients in amounts such that each actuation provides therapeutically effective dose, for example, a dose of salmeterol of 10mcg to 150mcg, preferably 50mcg and a dose of mometasone of 100mcg to 1.6mg, preferably 200mcg to 1mg, more preferably, 200mcg to 400mcg.

The pharmaceutical formulations according to the invention may further include other therapeutic agents for example anti-inflammatory agents such as other corticosteroids (e.g. fluticasone propionate, beclomethasone dipropionate,

budenoside, or triamcinolone acetonide), or NSAIDs (e.g. sodium cromoglycate, nedocromil sodium, PDE-4 inhibitors, leukotriene antagonists, iNOS inhibitors, tryptase and elastase inhibitors, beta-2 integrin antagonists and adenosine 2a agonists), or other β_2-adrenoreceptor agonists (such as salbutamol, formoterol, fenoterol or terbutaline and salts thereof), or anticholinergic agents (such as ipratropium, or tiotropium).

The formulations include those suitable for oral, parenteral (including subcutaneous, intradermal, intramuscular, intravenous and intraarticular), inhalation (including fine particle dusts or mists which may be generated by means of various types of metered dose pressurised aerosols, nebulisers or insufflators), rectal and topical (including dermal, buccal, sublingual and intraocular) administration although the most suitable route may depend upon for example the condition and disorder of the recipient. The formulations may conveniently be presented in unit dosage form and may be prepared by any of the methods well known in the art of pharmacy. All methods include the step of bringing the active ingredients into association with the carrier which constitutes one or more accessory ingredients. In general the formulations are prepared by uniformly and intimately bringing into association the active ingredients with liquid carriers or finely divided solid carriers or both and then, if necessary, shaping the product into the desired formulation.

Formulations for inhalation include powder compositions which will preferably contain lactose, and spray compositions which may be formulated, for example, as aqueous solutions or suspensions or as aerosols delivered from pressurised packs, with the use of a suitable propellant, e.g. dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, 1,1,1,2,3,3,3-heptafluoropropane, 1,1,1,2-tetrafluoroethane, carbon dioxide or other suitable gas. Suitable aerosol formulations include those described in EP 0372777 and WO93/11743. For suspension aerosols, the active ingredients should be micronised so as to permit inhalation of substantially all of the active ingredients into the lungs upon administration of the aerosol formulation, thus the active ingredients will have a particle size of less than 100 microns, desirably less than 20 microns, and preferably in the range 1 to 10 microns, for example, 1 to 5 microns.

Intranasal sprays may be formulated with aqueous or non-aqueous vehicles with the addition of agents such as thickening agents, buffer salts or acid or alkali to adjust the pH, isotonicity adjusting agents or anti-oxidants.

Capsules and cartridges or for example gelatin, or blisters of for example laminated aluminium foil, for use in an inhaler or insuflator may be formulated containing a powder mix of the active ingredients and a suitable powder base such as lactose or starch. In this aspect, the active ingredients are suitably micronised so as to permit inhalation of substantially all of the active ingredients into the lungs upon administration of the dry powder formulation, thus the active ingredients will have a particle size of less than 100 microns, desirably less than 20 microns, and preferably in the range 1 to 10 microns.

Solutions for inhalation by nebulation may be formulated with an aqueous vehicle with the addition of agents such as acid or alkali, buffer salts, isotonicity adjusting agents or antimicrobials. They may be sterilised by filtration or heating in an autoclave, or presented as a non-sterile product.

Preferred unit dosage formulations are those containing a pharmaceutically effective dose, as hereinbefore recited, or an appropriate fraction thereof, of the active ingredient. Thus, in the case of formulations designed for delivery by metered dose pressurised aerosols, one actuation of the aerosol may deliver half of the therapeutically effective amount such that two actuations are necessary to deliver the therapeutically effective dose.

It should be understood that in addition to the ingredients particularly mentioned above, the formulations of this invention may include other agents conventional in the art having regard to the type of formulation in question. Furthermore, the claimed formulations include bioequivalents as defined by the US Food and Drugs Agency.

For a better understanding of the invention, the following Examples are given by way of illustration.

EXAMPLES

A: Metered Dose Inhalers

Example 1

	Per actuation
Salmeterol Xinafoate	36.3 microgram
Mometasone	200 microgram
1,1,1,2-Tetrafluoroethane	to 75.0mg

The micronised active ingredients are weighed into an aluminium can, 1,1,1,2-tetrafluoroethane is then added from a vacuum flask and a metering valve is crimped into place.

Similar methods may be used for the formulation of Examples 2 and 3:

Example 2

	Per actuation
Salmeterol Xinafoate	36.3 microgram
Mometasone	100 microgram
1,1,1,2-Tetrafluoroethane	to 75.0mg

Example 3

	Per actuation
Salmeterol Xinafoate	36.3 microgram
Mometasone Furoate	100 microgram
1,1,1,2-Tetrafluoroethane	to 37.50mg

Example 4

	Per actuation
Salmeterol Xinafoate	36.3 microgram
Mometasone Furoate	100 microgram
1,1,1,2-Tetrafluoroethane	to 75.0mg

Salmeterol xinafoate (5.8mg) and mometasone furoate (16.0mg) were weighed directly into an 8ml aluminium canister coated internally with a PTFE/PES polymer blend as described in WO96/32150. A Valois DF60 metering valve was crimped into place, 1,1,1,2-tetrafluoroethane (to 12g) added and the filled canister was sonicated for at least five minutes. The resultant aerosol delivered 25 microgram salmeterol (as the xinafoate salt) and 100 microgram mometasone furoate per actuation.

An alternative method for preparing the formulations described in Examples 1 to 4 involves mixing the micronised medicaments and a portion of the propellant in a pressure vessel. An aliquot of the resultant suspension, followed by an aliquot of propellant is filled into a closed canister via the metering valve.

B: Dry Powder Inhalers

Example 5

	Per cartridge or blister
Salmeterol Xinafoate	72.6 microgram
Mometasone	200 microgram
Lactose Ph. Eur.	to 12.5mg or to 25.0mg

The active ingredients are micronised and bulk blended with the lactose in the proportions given above. The blend is filled into hard gelatin capsules or cartridges or in specifically constructed double foil blister packs to be

administered by an inhaler such as a Rotahaler, Diskhaler, or Diskus inhaler (each of these being a Trademark of Glaxo Group Limited).
Similar methods may be used for the formulations of Example 6:

Example 6

	Per cartridge or blister
Salmeterol Xinafoate	72.6 microgram
Mometasone	100 microgram
Lactose Ph. Eur.	to 12.5mg or to 25.0mg

Example 7

	Per blister
Salmeterol Xinafoate	72.5 microgram
Mometasone Furoate	200.0 microgram
Lactose Ph. Eur.	to 25.0mg

The active ingredients were micronised and bulk blended with the lactose in the proportions given above. The blend was then filled into specifically constructed double foil blister packs to be administered by a Diskhaler (Trademark of Glaxo Group Limited).

C: Suspension for nebulisation

Example 8

	Quantity (mg)
Salmeterol Xinafoate (micronised)	0.0725
Mometasone Furoate (micronised)	0.20
Polysorbate 20	0.14
Sorbitan Monolaurate	0.018
Monosodium Phosphate dihydrate	18.80
Dibasic Sodium Phosphate anhydrous	3.50
Sodium Chloride	9.60
Water for injection	to 2.00 ml

D: Aqueous nasal spray

Example 9

	Quantity[1] (%w/w)
Salmeterol Xinafoate (micronised)	0.03625
Mometasone Furoate (micronised)	0.05
Dextrose Anhydrous	5.00
Microcrystalline cellulose and carboxymethylcellulose sodium	1.50
Phenylethyl alcohol	0.25
Benzalkonium Chloride solution (50%w/v)	0.04v/w
Polysorbate 80	0.005
Purified water	to 100

[1] Based on 100mg suspension per actuation

E: Intranasal dry powder

Example 10

	Per blister
Salmeterol Xinafoate (micronised)	72.50 microgram
Mometasone Furoate (micronised)	100.00 microgram
Potato Starch NF/BP	to 10mg

Cascade Impaction Data

The particle size distribution of the aerosol formulations according to the invention may be measured by conventional techniques, such as cascade impaction (for example as defined in US Pharmacopoeia, 23/NF18 General Test <601>, pages 1762 - 1765).

Results

For the product of Example 4, the Cascade Impaction data were as follows:

Salmeterol:

Sample	Sample 1 Total %	Sample 2 Total %	Mean Total %
Device	12.1	15.6	13.8
Throat	35.2	36.5	35.8
Stage 0	6.5	4.1	5.3
Stage 1	2.4	2.0	2.4
Stage 2	2.8	2.5	2.8
Stage 3	13.0	11.5	12.2
Stage 4	15.8	15.6	15.9
Stage 5	11.3	11.5	11.4
Stage 6	0.8	0.8	0.8
Stage 7	0.0	0.0	0.0
Filter	0.0	0.0	0.0
Total	100.0	100.0	100.0

Sample	Sample 1 Total %	Sample 2 Total %	Mean Total %
Total Ex-device	87.9	84.4	86.2
FPM Sum Stages 3-5	40.1	38.5	39.4

Mometasone:

Sample	Sample 1 Total %	Sample 2 Total %	Mean Total %
Device	6.0	9.2	7.7
Throat	34.0	38.0	36.0
Stage 0	6.2	3.9	5.0
Stage 1	2.6	2.4	2.5
Stage 2	3.0	2.7	2.8
Stage 3	19.5	16.3	17.9
Stage 4	18.6	17.2	17.9
Stage 5	9.3	9.3	9.3
Stage 6	0.7	0.6	0.7
Stage 7	0.2	0.2	0.2
Filter	0.0	0.2	0.1
Total	100.0	100.0	100.0
Total Ex-device	94.0	90.8	92.3
FPM Sum Stages 3-5	47.3	42.8	45.0

These data are also presented graphically in Figure 1.

For the product of Example 7, the Cascade Impaction data were as follows

Salmeterol:

Sample	Disk 2 Total %	Disk 4 Total %	Mean Total %
Throat	16.4	16.0	16.3
Pre-sep & Stage 0	51.9	50.6	51.2
Stage 1	5.0	5.5	5.2
Stage 2	3.9	4.0	3.9
Stage 3	10.6	11.2	11.0
Stage 4	8.2	8.1	8.0
Stage 5	2.8	3.5	3.1
Stage 6	0.8	0.7	0.8
Stage 7	0.6	0.2	0.5
Filter	0.0	0.0	0.0
Total	100.0	100.0	100.0
FPM Sum Stages 1-5	30.3	32.4	31.5

Mometasone:

Sample	Disk 2 Total %	Disk 4 Total %	Mean Total %
Throat	15.2	15.0	15.1
Pre-sep & Stage 0	48.7	46.2	47.4
Stage 1	6.4	6.7	6.5
Stage 2	5.5	6.0	5.8
Stage 3	13.2	14.6	13.9
Stage 4	7.1	7.5	7.3
Stage 5	2.6	3.1	2.9
Stage 6	0.8	0.8	0.8
Stage 7	0.5	0.3	0.4
Filter	0.0	0.0	0.0
Total	100.0	100.0	100.0
FPM Sum	34.8	37.8	36.4

Sample	Disk 2 Total %	Disk 4 Total %	Mean Total %
Stages 1-5			

These data are also presented graphically in Figure 2.

Claims

1. A pharmaceutical formulation comprising salmeterol or a pharmaceutically acceptable salt, solvate, or physiologically functional derivative thereof and mometasone or a pharmaceutically acceptable salt, solvate, or physiologically functional derivative thereof, and a pharmaceutically acceptable carrier or excipient, and optionally one or more other therapeutic ingredients.

2. A pharmaceutical formulation comprising salmeterol xinafoate and mometasone furoate, and a pharmaceutically acceptable carrier or excipient, and optionally one or more other therapeutic ingredients.

3. A pharmaceutical formulation according to claim 1 or 2 which is suitable for administration by inhalation.

4. A pharmaceutical formulation according to any of claims 1 to 3 wherein the pharmaceutically acceptable carrier or excipient is lactose.

5. A pharmaceutical formulation according to any of claims 1 to 3 wherein the pharmaceutically acceptable carrier or excipient comprises 1,1,1,2-tetrafluoroethane and/or 1,1,1,2,3,3,3- heptafluoropropane.

6. A method for the prophylaxis or treatment of a clinical condition in a mammal, such as a human, for which a selective β_2-adrenoreceptor agonist and/or antiinflammatory corticosteroid is indicated, which comprises administration of a therapeutically effective amount of a pharmaceutical formulation according to any one of claims 1 to 5.

7. A method according to claim 6 wherein the clinical condition is a disease associated with reversible airways obstruction such as asthma, chronic obstructive pulmonary disease (COPD), respiratory tract infection or upper respiratory tract disease.

FIGURE 1

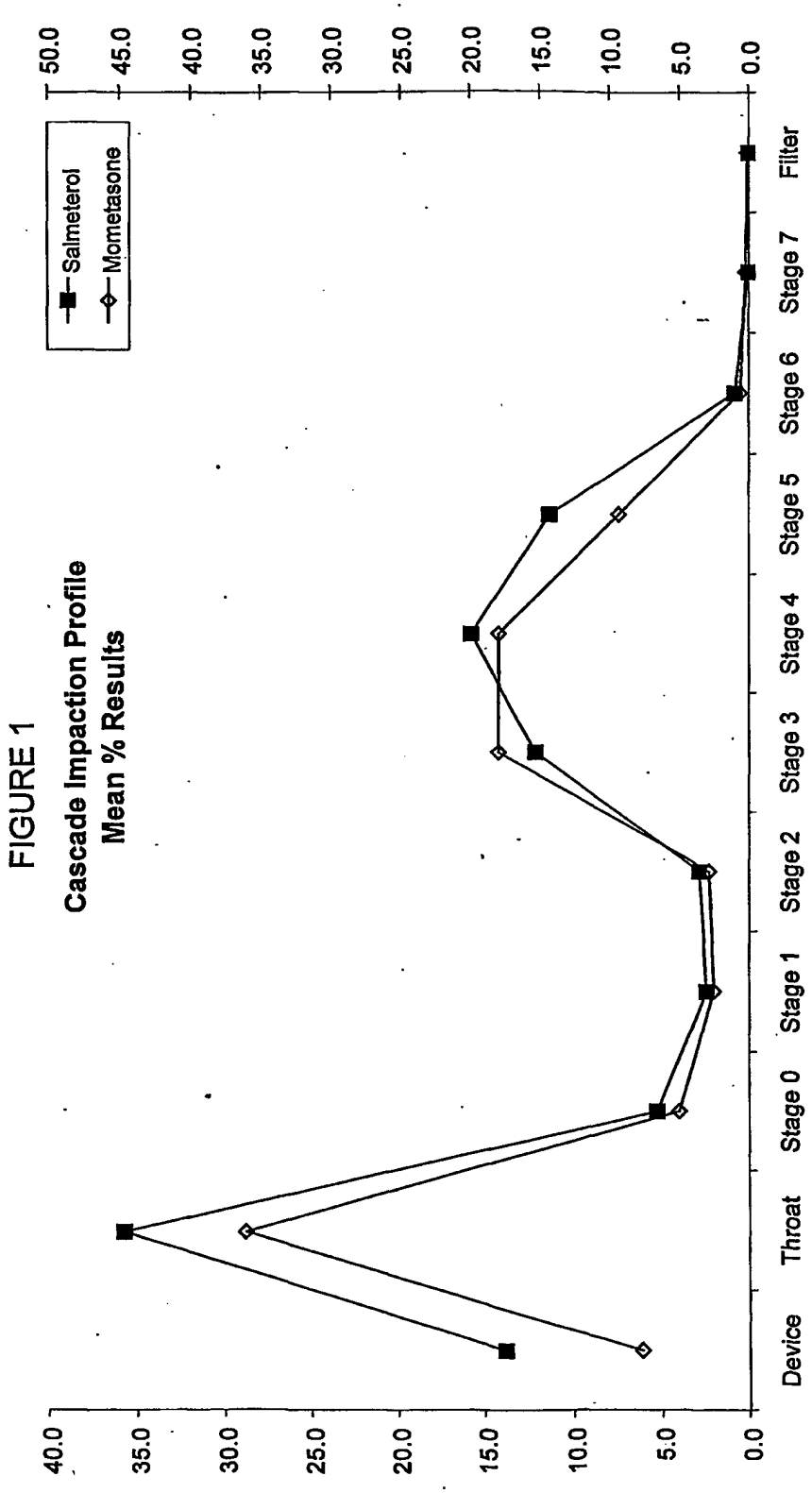
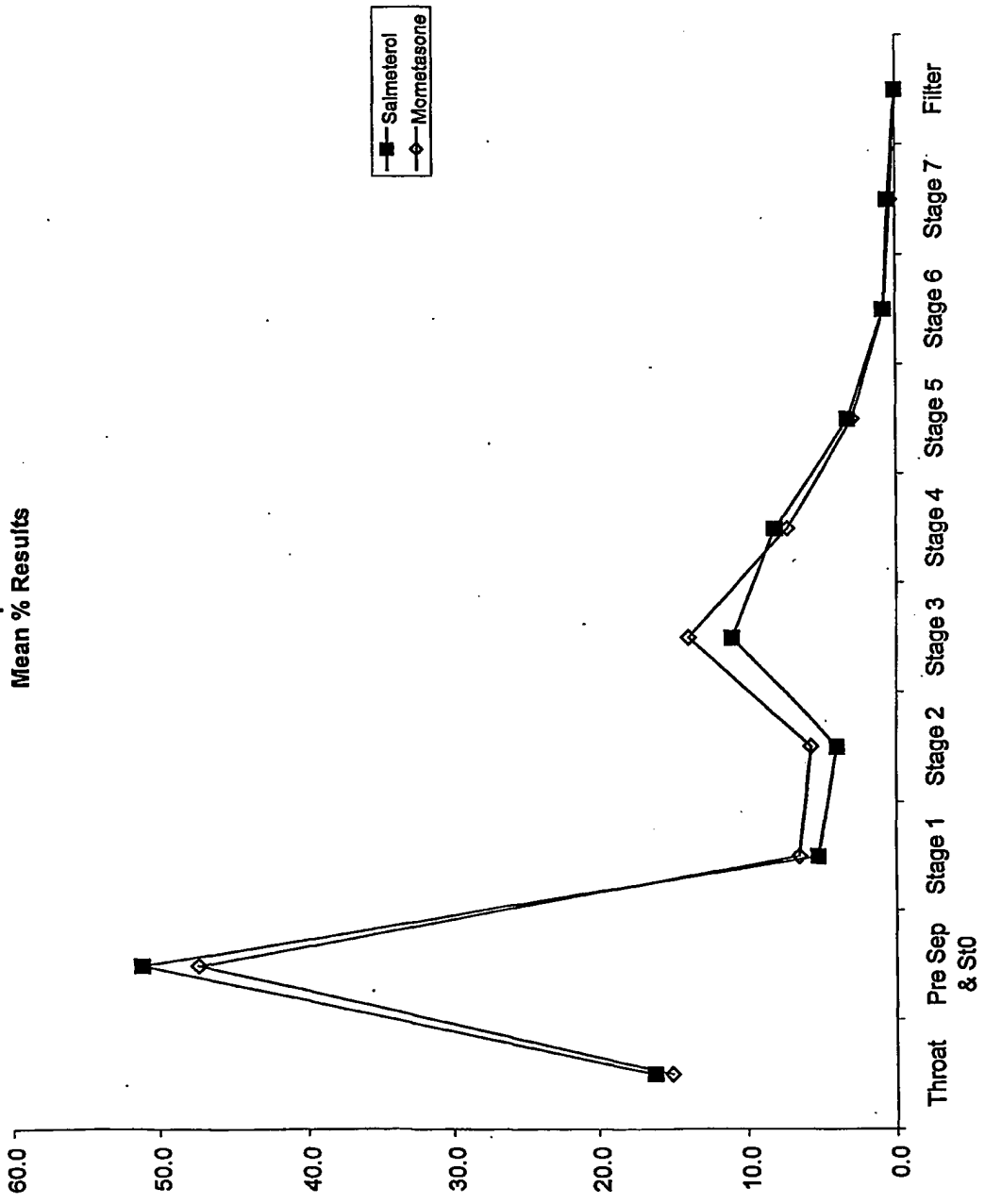

Cascade Impaction Profile
Mean % Results
Salmeterol
Mometasone
50.0
45.0
40.0
35.0
30.0
25.0
20.0
15.0
10.0
5.0
0.0
Device
Throat
Stage 0
Stage 1
Stage 2
Stage 3
Stage 4
Stage 5
Stage 6
Stage 7
Filter

FIGURE 2

Cascade Impaction Profile
Mean % Results



INTERNATIONAL SEARCH REPORT

Int al Application No
PCT/GB 01/01637

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/575 A61K31/137 A61P11/06 //(A61K31/575,31:137)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, MEDLINE, BIOSIS, CHEM ABS Data, EMBASE, PAJ

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 98 41193 A (SCHERING CORP) 24 September 1998 (1998-09-24) cited in the application claims 1,5,46-50	1-7
Y	US 4 472 393 A (SHAPIRO ELLIOT L) 18 September 1984 (1984-09-18) cited in the application the whole document	1-7

-/--

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

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8 August 2001	04/09/2001

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INTERNATIONAL SEARCH REPORT

Int[illegible]al Application No
PCT/GB 01/01637

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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